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Axonal protein synthesis: a potential target for pain relief?

Ilona Obara[1,2], Sandrine M Géranton[1] and Stephen P Hunt[1]

Research on the role of axonal protein synthesis in the regulation of nociceptive mechanisms has grown significantly over the past four years. Recent advances include evidence that local translation of mRNA can occur in adult primary afferents under the control of the mammalian target of rapamycin (mTOR) and the extracellular signal-regulated kinase (ERK) signaling pathways. Studies investigating the effect of mTOR and ERK pathway inhibitors in a number of pain models suggest that these signaling pathways may act independently, depending on the type of sensory afferents studied. The evidence that nociception can be regulated at the level of mRNA translation in nociceptors has important implications for the understanding of the mechanisms of nociceptive plasticity and therefore for therapeutic interventions in chronic pain conditions.

Addresses
[1] Department of Cell and Developmental Biology, University College London, London WC1E 6BT, United Kingdom
[2] Department of Pain Pharmacology, Institute of Pharmacology, Polish Academy of Sciences, 31-343 Krakow, Poland

Corresponding author: Obara, Ilona (i.obara@ucl.ac.uk)

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Introduction

The idea that mature adult axons have the capacity for local protein synthesis independently from the cell body has gradually been gaining acceptance. Piper and Holt [1] reflected that the demands of an axonal process of up to one meter in length, as in human primary sensory neurons, would be extremely difficult to fulfill just relying purely on proteins synthesized in the neuronal cell body and transported along the axon. Even using fast axoplasmic transport (50–200 mm/day), proteins would take hours or days to arrive at the distal segments of the axon embedded within peripheral tissues. Local mRNA translation in axons would therefore appear to have enormous advantages and permit a reasonably rapid response to changing conditions. Evidence for local mRNA translation is particularly strong in the growth cones of developing axons or in regenerating adult sensory axons, where local protein synthesis is seen as a response to environmental cues [2–4,5•,6]. Recently, studies have suggested that local mRNA translation occurs in adult primary afferent axons and is thought to be functionally important in nociception [7•,8•,9–13,14•,15,16].

Nociceptors and nociception

Primary afferents are divided into myelinated A-fibers that signal noxious or innocuous stimuli and unmyelinated C-fibers that are largely nociceptors. A-nociceptors mediate 'first' pain perceived as rapid and sharp and C-fibers signal 'second' pain, delayed, diffuse, and dull [17,18]. Nociceptors innervate the skin, muscle, joints, and viscera that selectively respond to noxious or potentially tissue-damaging stimuli. The most common nociceptor in the skin is the C-polymodal nociceptor, which responds to thermal, mechanical, and chemical stimulation [19]. Skin also contains modality-selective nociceptors such as C-heat and C-mechano-cold nociceptors while joints and viscera are innervated by C-nociceptors responding to both mechanical and chemical stimulation [18]. Finally, a subset of C-nociceptors, chemosensitive but relatively insensitive to mechanical stimuli in the absence of tissue injury, is referred to as 'silent' nociceptors, or as mechanically insensitive afferents [18]. One essential characteristic of most nociceptors is that they sensitize which results in a reduction in their activation threshold and an increase in the magnitude of the response to noxious stimulation [17,18]. For example, inflammation or tissue injury provokes the release of a variety of cytokines (i.e. interleukin-6, IL-6) and growth factors (i.e. nerve growth factor, NGF) that act on and increase the sensitivity of a subset of nociceptors to noxious stimulation resulting in primary hyperalgesia [18]. However, an important subset of A-nociceptors and some C-nociceptors, terminating away from the site of injury, do not sensitize but contribute to the increased mechanical sensitivity in the undamaged area around the site of injury resulting in secondary hyperalgesia [20•]. This secondary spread of sensitivity away from the site of primary injury is a product of central processing. Thus injury responsive C-fibers set up central sensitization in the dorsal horn, a mechanism that leads to the amplification of the subsequent response of Aδ-fibers and some Aβ-fibers (involved in touch), resulting in increased pain or enhanced sensitivity to pinprick and light touch [20•,21]. Below we summarize the evidence that local protein synthesis may regulate the excitability of A-nociceptors and C-nociceptors but through different signaling pathways.

Translation and sensory axons

Translation of mRNA takes place in three steps, initiation, elongation, termination, and is a rapid and

reversible process spatially controlled by a large number of upstream kinases [15]. The activity of these kinases can be modulated by selective inhibitors or by endogenous signaling factors that act on these pathways (Figure 1).

The major protein kinase that regulates initiation of translation is the mammalian target of rapamycin (mTOR), a critical downstream target of the phosphatidylinositol-3 kinase (PI3K) pathway, which signals to eukaryotic initiation factor (eIF) eIF4E and eIF4G and the eIF4E binding protein (4EBP) [15,22]. mTOR plays a major role in regulating cell growth and metabolism in eukaryotic cells and forms two distinct complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) [22,23] (details in Figure 1a and b).

Another kinase regulating mRNA translation is the extracellular regulated kinase (ERK; Figure 1c). ERK controls the initiation of translation by acting on eIF4E but can also indirectly engage mTORC1 signaling through tuberous sclerosis complex 2 (TSC2) [15,24].

In the periphery, the necessary machinery for the mRNA translation is present in peripheral sensory axons [1,8•,13,16,25]. Ribosomes, while difficult to detect using electron microscopy, have been observed using immunohistochemical approaches and are derived from the cell body although it was recently shown that ribosomes can be transferred from Schwann cells to axons [1,26•,27•]. There is also evidence for the transport of subsets of mRNA traveling down the axon in association with RNA binding and transport proteins such as staufen and fragile X mental retardation protein [28,29].

Local translation and nociception

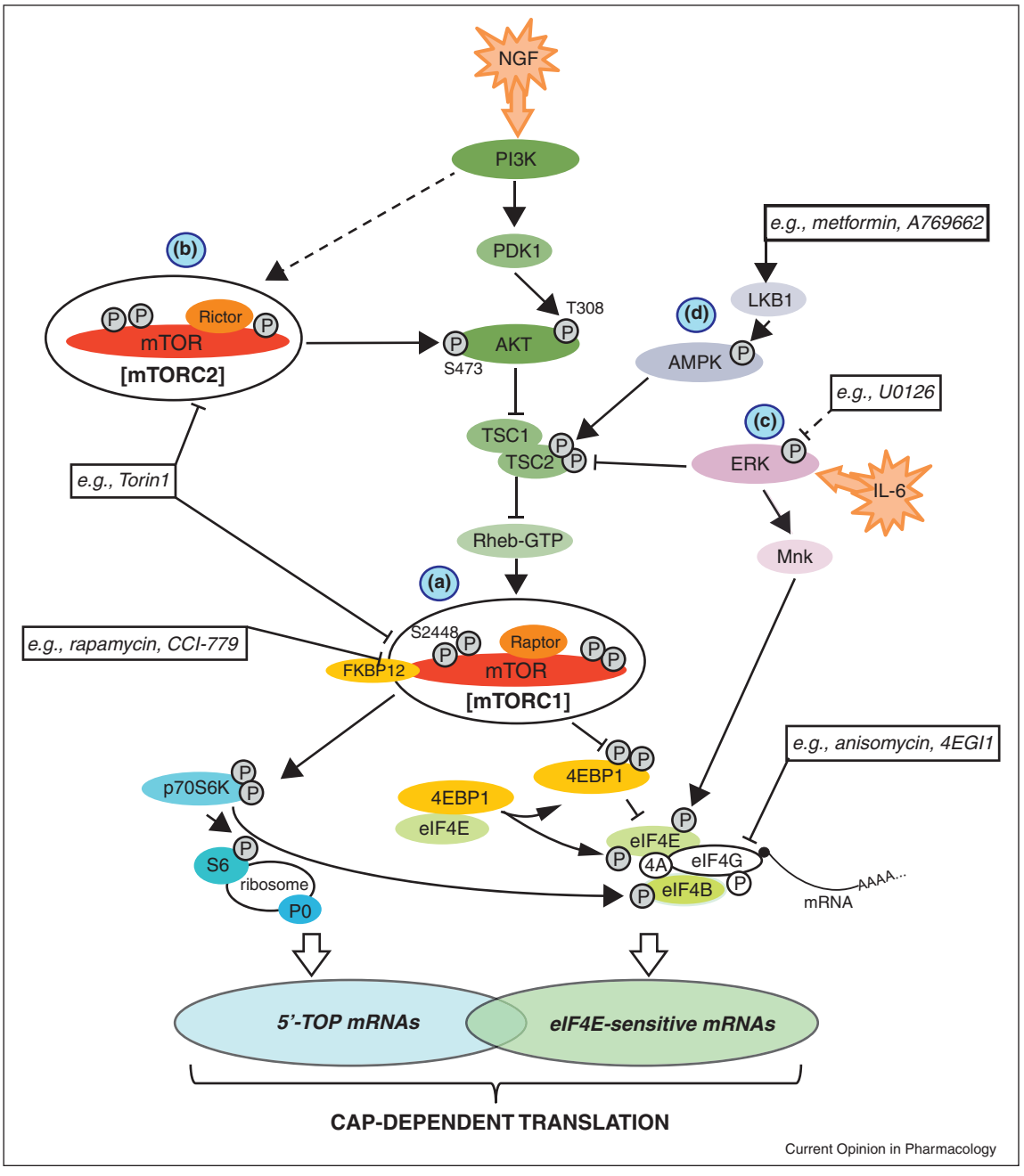
Several studies have concluded that mRNA translation in sensory axons plays a role in regulating peripheral nociception [7•,8•,9–13,14•,15,16]. Both mTOR and ERK pathways are critical for neuronal plasticity and it is suggested that both are activated within axons after noxious stimulation, although possibly through different mechanism and in different type of sensory afferents [7•,8•,13,14•,16] (Figures 1 and 2).

Specifically, it has recently been suggested that two major algogens, IL-6 and NGF, signal through two distinct pathways to enhance translation in sensory neurons by converging onto the eIF4F complex [14•]. While sensitization of nociceptors by IL-6 or coinjection of IL-6 and NGF produces enhanced mechanical hypersensitivity that can be reduced by blockers of translation (e.g. anisomycin, 4EGI1) or of the ERK pathway (e.g. U0126) [14•], *in vitro* activation of dissociated dorsal root ganglion (DRG) neurons by NGF is blocked by the mTORC1 inhibitor rapamycin, although this was not confirmed *in vivo* [14•] (Figure 1). These results suggest that ERK-driven local mRNA translation may support peripheral sensitization. However, while local NGF injection causes sensitization, the evidence that NGF activates local mRNA translation *in vivo* has not been presented [14•].

In vivo evidence is even more puzzling. The hallmark of peripheral sensitization is increased thermal sensitivity thought to be supported by ERK activation at the level of the cell body and by a subsequent synthesis of the TRPV1 receptor and its transport to the axon terminals in inflamed cutaneous tissue, but not by local translation [30]. Moreover, thermal sensitivity of inflamed tissue is not reduced by local injection of mTOR inhibitors, rapamycin or its analog temsirolimus — CCI-779 [8•,13], suggesting that local translation does not support peripheral sensitization. Although intrathecal injection of rapamycin has been shown to produce variable effects on thermal thresholds, this may be the result of a direct modulation of central processing [7•,9,10,12]. In contrast to thermal hyperalgesia, increased mechanical sensitivity following inflammation has been shown to be influenced by local inhibitors that influence both mTOR and ERK pathways [7•,8•,9–13,14•]. How is it possible that thermal and mechanical sensitivity can be independently regulated by local mRNA translation in nociceptors? It may be that thermal and mechanical stimulation activate different nociceptor populations [33], but given the physiological characterization of C-nociceptors this seems unlikely. Alternatively, there may be direct modulation of molecular determinants of mechanosensation in primary afferent nociceptors.

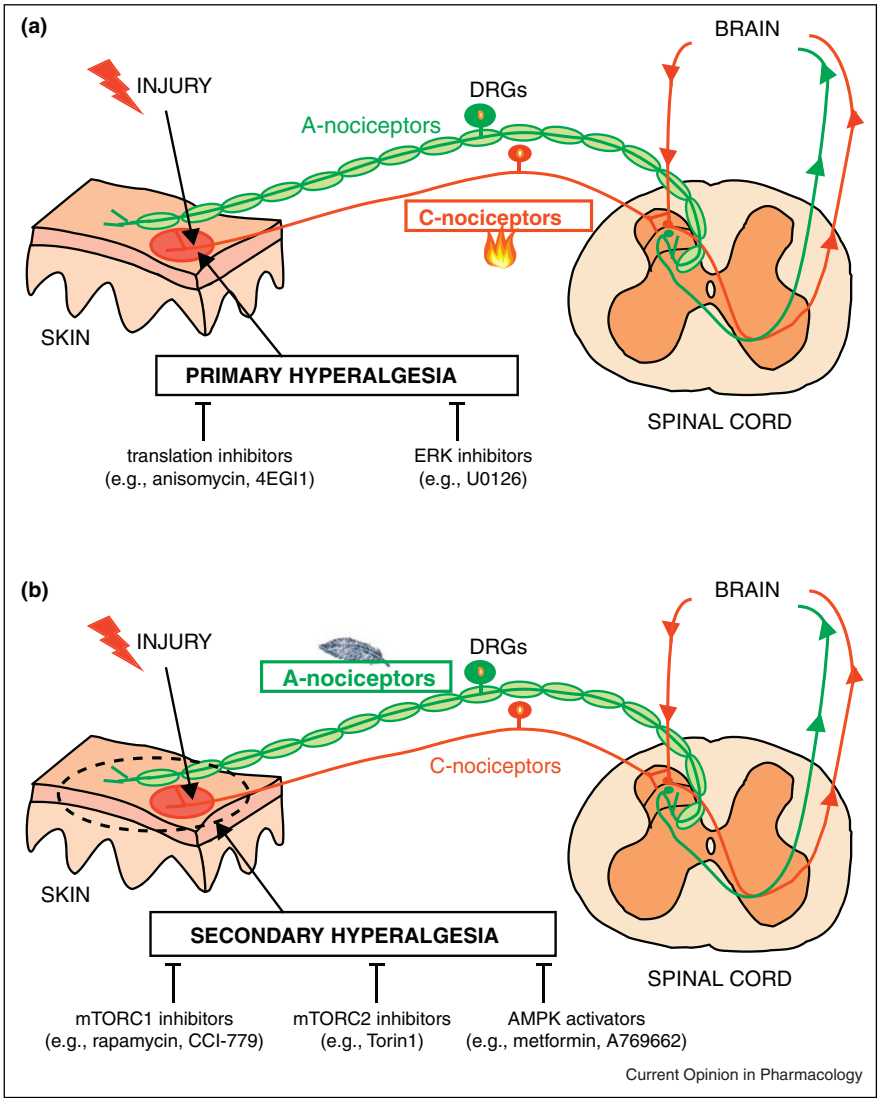
Another explanation arose from the study of the distribution of the translational apparatus in primary afferents. Specifically, one of the active forms of mTOR (phosphorylated at serine 2448 [31]) and other downstream components of the translational machinery were localized to subsets of myelinated sensory fibers, and also to a small number of unmyelinated fibers in rodent cutaneous tissue [7•,8•,13,16]. In line with this evidence, electromyographic studies showed that rapamycin reduced the sensitivity of myelinated A-nociceptors [7•,8•] also known to be important for the increased mechanical sensitivity that follows injury (i.e. secondary hyperalgesia) [20•]. Behavioral studies on capsaicin model further confirmed that local treatment with mTOR inhibitors (i.e. spinal or intraplantar administration of rapamycin or CCI-779) blunted the heightened response to mechanical stimulation that develops only *around* the site of injury (mediated by capsaicin-insensitive A-nociceptors), while the acute pain (transmitted by capsaicin-sensitive polymodal A-nociceptors and C-nociceptors) was entirely unaffected [7•,8•,13]. It is important to note that these A-fibers and probably the small set of C-fibers that contribute indirectly to increased mechanical sensitivity do not sensitize and that the sensitivity of these fibers is *maintained* by ongoing mTOR-mediated local protein

Figure 1



Regulation of mRNA translation in primary afferents. Translation of mRNA is controlled by a large number of kinases. mTORC1 **(a)**: contains raptor, is sensitive to the selective inhibitor rapamycin/CCI-779 that binds to FKBP12 and is controlled via the PI3K/Akt/mTOR pathway [22,23]. mTORC2 **(b)**: contains the protein rictor, is resistant to rapamycin/CCI-779 and is thought to modulate growth factor signaling by phosphorylating Akt kinases at serine 473 [22,23]. Inhibition of mTORC1 with rapamycin/CCI-779/Torin1 (a) or mTORC2 with Torin1 (b) in primary afferents prevents these kinases from phosphorylating its target proteins and thus presumably prevents the initiation of CAP dependent translation of mRNAs [7•,8•,13]. Phosphorylation of 4EBP, which is a negative regulator of eIF4F complex formation, leads to its dissociation from eIF4E and binding of eIF4E to eIF4G. While the phosphorylation of 4EBP have been shown to mainly regulate the CAP translation of so-called eIF4E sensitive mRNAs characterized by long and complex 5′UTR, the activation of p70S6K has been linked to the CAP translation of subpopulations of mRNAs carrying a 5′ terminal oligopyrimidine tract (5′ TOP), such as ribosomal proteins, poly(A) binding protein and translation elongation factors required for new protein synthesis. It has been suggested that *in vitro* NGF signals to the translational machinery through eIF4G, resulting in rapid changes in mRNA translation in sensory neurons [14•]. In contrast to NGF, IL-6 signals to the translational machinery through the ERK/Mnk/eIF4E signaling pathway and this is inhibited in primary afferents by the selective inhibitor of the MAPK/ERK kinase — U0126 [14] **(c)**. In addition, ERK phosphorylation can lead to TSC1/TSC2 dissociation and impairment of the ability of TSC2 to inhibit mTORC1 signaling [24]. In contrast, phosphorylation of TSC2 by AMPK results in the activation of TSC1/TSC2 and subsequent inactivation of mTORC1 [35] **(d)**. Thus, *in vitro* AMPK activation by metformin/A769662 in sensory neurons leads to inhibition in mTORC1 activity [35] and eIF4F complex formation [16]. *In vivo* AMPK activation by metformin inhibits nascent protein synthesis in damaged nerve [16].

Figure 2



Regulation of the sensitivity of different type of sensory afferents by mTOR and ERK signaling pathways. **(a)** Tissue injury provokes the release of a variety of cytokines (i.e. IL-6) and growth factors that increase the sensitivity of a subset of C-nociceptors to noxious stimulation resulting in primary hyperalgesia [18]. This increased sensitivity of C-nociceptors is reduced by blockers of translation (e.g. anisomycin, eEGI1) or of the ERK pathway (e.g. U0126) [14•]. mTOR is largely absent from C-fibers and primary hyperalgesia is unimpaired by mTOR inhibitors [7•,8•,13]. **(b)** An important subset of A-nociceptors (and some C-nociceptors), terminating away from the injury and expressing mTOR [7•,8•,13], do not sensitize but contribute to the increased mechanical sensitivity seen in the undamaged area surrounding the site of injury. This phenomenon is called secondary hyperalgesia and is a product of central processing [20•]. Administration of mTORC1 or/and mTORC2 inhibitors (e.g. rapamycin, CCI-779, Torin1) reduces mechanical sensitivity, in part, by reducing the sensitivity of A-nociceptors [7•,8•,13]. Also AMPK activators (e.g. metformin, A769662) decrease secondary hyperalgesia [14•].

synthesis (Figure 2). In fact, recently a group of low threshold C-fibers that do not sensitize but contribute to post-injury mechanical hypersensitivity was identified [21,32,33].

Taken together, the emerging data imply that mTOR-mediated translation is primarily restricted to subsets of A-fibers and only some C-fibers while ERK mediated local mRNA translation is found in C-fibers [7•,8•,13,14•]. Locally administered mTOR inhibitors reduce mechanical sensitivity, in part, by reducing the sensitivity of A-nociceptors [7•,8•,13]. In contrast, mTOR is largely absent from C-fibers and primary sensitization, that is generated by these nociceptors, is to a great extent unimpaired by mTOR inhibitors but not by ERK inhibitors [14•] (Figure 2).

The damaged peripheral nerve, local translation and chronic pain

Amplification of capsaicin-insensitive A-fibers signals by sensitized dorsal horn neurons accounts for the increased mechanical sensitivity to noxious stimulation and hypersensitivity to non-noxious stimulation that are clinical features of chronic pain, particularly neuropathic pain resulting from the injury of peripheral nerve [34]. There is recent evidence for reorganization of translation pathways and machinery in damage nerve that includes enhanced mTOR activity and phosphorylation of its downstream targets and increased eIF4F complex formation [16]. Given that: first, subsets of A-nociceptors express mTOR [7•,8•,13], second, *in vitro* rapamycin amplified the electrical activation threshold of Aδ-fibers in dorsal roots [7•]; three, peripheral, spinal or systemic injection of rapamycin or CCI-779 inhibited the activation of downstream targets of mTORC1 in dorsal roots and dorsal horn [7•,8•,13] it is not surprising that mTORC1 inhibitors substantially alleviated persistent pain states. Specifically, inhibition of mTORC1 with rapamycin or CCI-779 locally (spinal, intraplantar) or systemically reduced mechanical hypersensitivity in neuropathic pain, in part, by reducing the sensitivity of A-nociceptors [7•,8•,13]. In addition, it has been shown that 5′adenosine monophosphate-activated protein kinase (AMPK) activator, metformin, led to mTOR inhibition and a reduction in translation initiation [35] (Figure 1d). In rodents metformin and A769662 also inhibited nascent protein synthesis in damage nerve and reduced mechanical hypersensitivity in neuropathic pain [16].

Rapamycin and its analogs (e.g. CCI-779) have been used clinically as anticancer and immunosuppressant drugs and have a relatively mild side-effect profile that would support their long-term treatment for chronic pain [36]. Indeed, chronic systemic administration of CCI-779 did not influence the body weight or locomotor co-ordination or induce neural toxicity when administered daily for 6 days. Most importantly, chronic systemic treatment with CCI-779 inhibited the mTORC1 pathway in sensory axons and in dorsal horn and reduced mechanical and cold hypersensitivity after peripheral nerve injury without affecting the nociceptive threshold in naive controls [13]. In addition, Torin1, a novel ATP-competitive inhibitor targeting both mTORC1 and mTORC2 pathways [37], reduced the response to mechanical and cold stimuli in neuropathic pain after its chronic systemic administration [13].

Recent observations suggest that increased local synthesis of ion channels and receptors in the peripheral axons of DRG neurons and in the neuroma of the damaged nerve could facilitate nociceptive signal generation and spontaneous discharge after nerve injury. In fact, it was reported that injury resulted in elevated axonal excitability and increased NaV1.8 in sciatic nerves suggesting that axonal accumulation of NaV1.8 mRNA may play a role in the pathogenesis of neuropathic pain [38]. However, as sensitivity to blockers of mRNA translation was not reported, the precise function of local protein synthesis as a target for therapeutic intervention in chronic pain still needs to be identified.

Conclusions and future directions

The available evidence implies that local mRNA translation can occur in primary afferents under the control of the mTOR and ERK pathways. One form of activated mTOR is restricted to A-nociceptors and a small subset of C-fibers that signal the secondary changes in sensitivity following injury while ERK modulated local protein synthesis regulates the sensitization of C-nociceptors by inflammatory mediators [7•,8•,13,14•]. These findings emphasize, therefore, the importance of the mTOR and ERK pathways as a potential target for pain control. However, despite the axonal localization of the translational machinery and evidence for its functional implication in nociception, it remains unclear which mRNAs are transported and translated in axons. *In vitro* studies on developing or regenerating axons listed several thousand potential transcripts including cytoskeletal, mitochondrial and signaling proteins. In a comparison microarray study embryonic and adult DRG axons were found to contain a significant number of transcripts that are uniquely enriched at each developmental stage, with over 1100 transcripts present only in embryonic and over 1400 present only in adult axons [39]. In a second *in vitro* study, using a sequential analysis of gene expression (SAGE) analysis of sympathetic axons it was shown that over 11 000 transcripts could be detected. Myo-inositol monophosphate-1 mRNA, chosen for further analysis, was shown to be under the control of exogenously applied NGF [40•]. In another *in vitro* study acute inhibition of protein synthesis with emetine or cyclohexamide in sympathetic axons resulted in a decrease in the membrane potential of axonal mitochondria suggesting that the axonal membrane potential may also be indirectly regulated by local translation of mRNA [41,42]. However, comparable *in vivo* studies have not been published and the precise mechanism for pain relief via modulation of axonal protein synthesis still remains to be determined.

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